THIAZOLYLUREA DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

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Kivonat

1437895 Thiazolyl-ureas and -thioureas EGYT GYOGYSZERVEGYESZETI GYAR 4 Nov 1974 [9 Nov 1973] 47689/74 Heading C2C Novel compounds of Formula I wherein R1 stands for a pyridyl group, R2 and R3 each stand for hydrogen or a lower alkyl group, Y stands for oxygen or sulphur, and R4 and R5 each stand for hydrogen, a lower alkyl group, allyl group, a C 3-6 cycloalkyl group, phenyl group or a halophenyl group, or R4 and R5 may form together with the adjacent nitrogen atom a heterocyclic group of the gen- eral Formul (X) or (XI) wherein n represents an integer of from 4 to 7, and Z stands for oxygen, or an =NH, =N-CH 3 or =N-C 6 H 5 group are prepared by one of the following methods (a) a compound of Formula II wherein X is halogen is reacted with a compound of Formula III or (b) a compound of Formula IV is reacted with R5(R6)N.C=Y, a compound of Formula XIII or an alkali metal cyanate or thiocyanate and a strong acid or (c) a compound of Formula VI wherein R6 is C 1-4 alkyl or phenyl is reacted with an amine R4NHR5 or (d) a compound of Formula IX is reacted with an amine R4NHR5 (e) a com- pound of Formula XII is reacted with an amine R4NHR5. Intermediates of Formula IX above are pre- pared either by reacting a compound of Formula IV above with CS 2 and dicyclohexyl carbodi- imide or by heating a compound of Formula VIII Cyclopropyl isothiocyanate is prepared by reacting cyclopropylamine with CS 2 and NaOH. 4 - (31 - Pyridyl) - thiazole - 2 - carboxylic acid azide is prepared by action of aqueous NaNO 2 on 4 - (31 - pyridyl)thiazole - 2 - carboxylic acid hydroxide obtained by action of hydrazine hydrate on the ethyl ester of the acid. Pharmaceutical compositions in conventional forms for oral, rectal or parenteral administra- tion and having anti-inflammatory and anti- ulcer activity comprises an above novel com- pound and a carrier or diluent.

Az adatok az esp@cenet adatbázisból származnak - l2

Leírás

(54) NEW THIAZOLYI,UREA DERIVATIVES AND PROCESS
FOR THE PREPARATION THEREOF
(71) We, EGYT GY6GYSZERVEG- Y0SZETI GYAR of 30, Keresztdri fit, Budapest X., Hungary, a body corporate organised under the laws of Hungary, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-
This invention relates to new thiazolylurea derivatives and pharmaceutical compositions containing the same, as well as to a process for the preparation thereof.

As known, several substituted urea and thiourea derivatives possess valuable pharmaceutical activities. Thus, for example, the urea and thiourea derivatives of 4-phenyl-2-amino- thiazole possess antiviral activity (see published
German Patent Application Nos. 2,132,431 and 2,144,683).

Several methods are known for the preparation of urea and thiourea derivatives
(Chem. Rev. 55, 181/1955/; Houben-Weyl,
Vol. VIII, 149-166, Georg Thieme Verlag,
Stuttgart, 1952; Houben-Weyl, Vol. IX, 884-899, Georg Thieme Verlag, Stuttgart,
1955). It is also known that when reacting w-bromo-acetophenone with thiobiuret, 1-(4'phenyl-thiazol-2-yl)-urea is obtained (Chem.

Ber. 99, 2937/1966/).

Now it has been found that new compounds possessing valuable pharmaceutical effects can be obtained by converting the amino group of 2-aminothiazole into an ureido or thioureido group, and introducing a pyridyl group into position 4 and optionally a lower alkyl group into position 5 of the thiazole ring.

Accordirgly, the invention relates to new substituted thiazolylurea and -thiourea derivatives having the general formula (I) and pharmaceutically acceptable acid addition salts thereof,

wherein
RI stands for a pyridyl group,
R2 and R3 each stand for hydrogen or an alkyl group having from 1 to 4 carbon atoms,
Y stands for oxygen or sulphur, and
R and R6 each stand for hydrogen, an alkyl group having from 1 to 4 carbon atoms, allyl group, a C cycloalkyl group, phenyl group or a halophenyl group, or
R4 and Rs may form, together with the adjacent nitrogen atom, a heterocyclic group of the general formula (X) or (XI),

wherein
n represents an integer of from 4 to 7, and
Z stands for oxygen, or an = NH,
=N-CH, or =N--C,H, group.

The invention relates further to a process for the preparations of compounds of the general formula (lj or acid addition salts thereof. According to the process of the invention
a) a haloacylpyridine hydrohalide of the general formula (II),

wherein

R2 and R2 each have the same meanings
as defined above and X stands for halo
gen, is reacted with a compound of the
general formul (III),

wherein
R3, R4, R5 and Y each have the same
meanings as defined above, or
b) a 2-aminothiazole of the general formula (IV),

wherein
Rl, R2 and R3 each have the same meanings
as defined above, is reacted with an
isocyanate or isothiocyanate of the general
formula (V),

wherein
R4, R5 and Y each have the same meanings
as defined above, or
c) a 2-aminothiazole of the general formula (IV), wherein R1, R2 and R3 each have the same meanings as defined above, is reacted
with an alkali metal cyanate or shiocyamate in the presence of a strong mineral or organic acid, or
d) a thiazol-2-yl-carbaminate or -thiocarbaminate of the general formula (VI),

wherein
R', R2 and R each have the same meanings
as defined above and R stands for an
alkyl group having 1 to 4 carbon atoms or
a phenyl group, is reacted with an amine
of the general formula (VII),

wherein
R4 and R each have the same meanings
as defined above, or
e) a thiazole-2-carboxylic azide of the general formula (VIII),

wherein
R1 and R2 each have the same meanings
as defined above, is converted by heat
treatment into a thiazol-2-yl-isocyanate
of the general formula (IX),

wherein
Rl and R2 each have the same meanings
as defined above and Y stands for oxygen,
and this compound is reacted, preferably
directly in the reaction mixture, with an
amine of the general formula (VIII),
wherein R4 and R5 each have the same
meanings as defined above, or
f) a 2-aminothiazole of the general formula (IV), wherein R1 and R2 each have the same meanings as defined above and R3 stands for hydrogen, is reacted with carbon disulphide and dicyclohexyl carbodiimide, and the obtained thiazoi-2-yl-isothiocyanate of the general formula (IX), wherein R1 and R each have the same meanings as defined above and Y stands for sulphur, is reacted with an amine of the general formula (VII), wherein R4 and
R5 each have the same meanings as defined above, or
g) a compound of the general formula (XII),

wherein
Rl, R2, R3 and Y each have the same

meanings as defined above, is reacted with
an amine of the general formula (VII),
wherein R4 and R5 each have the same
meanings as defined above, or
h) a 2-aminothiazole of the general formula (IV), wherein R', R and R3 each have the same meanings as defined above, is reacted with a carbamoylchloride or thiocarbamoyl- chloride of the general formula (XIII),

wherein
R4 and R6 each have the same meanings
as defined above, and, if desired, a free
base of the general formula (I) is con
verted into its pharmaceutically accept
able acid addition salt, or a salt is con
verted into the free base.

The above reactions are performed preferably in the presence of an inert solvent or diluent. As solvent or diluent preferably water, alcohols, such as methanol, ethanol or propanols, ether-type solvents, such as diisopropyl ether, di-n-butyl ether, ethyleneglycol dimethylether, dioxane or tetrahydrofuran, acid amide type solvents, such as methylformamide, dimethylformamide, methylacetamide, di methylacetamide, N-methyl-2-pyrrolidone or hexamethylphosphoric acid triamide, arornatic hydrocarbons, such as benzene, toluene or isomeric xylenes, haiogenated hydrocarbons, such as methylenechloride, ethylenechloride, chloroform or chlorobenzene, fuJiermore dimethylsulphoxide, or a mixture of these solvents can be used.The reactions are conducted at a temperature ranging from -200 C to +200 C.

In order to obtain optimum yield, process variant a) is carried out preferably at or near to the boiling point of the solvent (water or an aqueous alcohol) utilized, while the reactions according to process variant b) and f) are performed preferably in an ether-type solvent at the boiling point of the mixture, or in dimethylsulphoxide at 90 to 1000 C. In order to facilitate the reactions according to process variants b) and f) it is preferable to add triethylamine in an amount of 5 to 10% by weight, calculated for the reactants, to the reaction mixture. The reaction according to process variant c) can be performed in an aqueous medium in the presence of a strong mineral acid, iii some instances, however, it is preferred to carry out the reaction in benzene or toluene in the presence of trifluoroacetic acid.The reaction according to process variant d) can be performed in a dimethylsulphoxide medium at room temperature in the presence of an alkali metal (e.g. sodium or lithium) or an alkali metal hydride (e.g. sodium or lithium hydride); one may also proceed, however, by reacting a compound of the general formula (VI) with an excess of the respective amine with or without a solvent medium. In this latter instance, when an amine with a low boiling point is used, the reaction is preferably carried out in a closed vessel under superatmospheric pressure. The reaction according to process varient e) is performed preferably in the presence of an aromatic solvent, at or near to the boiling point of the solvent utilized.

When proceeding according to process variants g) or h) the reaction is preferably carried out in a chlorinated hydrocarbon medium. The most preferred acid binding agent for the reaction of process variant g) is the excess of the respective amine reactant, while when proceeding according to process variant h), preferably a tertiary organic base, such as pyridine, a-picoline or triethylamine is used as acid binding agent The temperature of the reaction mixture is initially maintained at a low value, optionally by external cooling, then the reaction is completed at room temperature, or optionally by heating the mixture up to
1000
C.

The reactants are applied generally in stoichiometric amounts, in some instances, however, it is preferable to use the more easily accessible reagent in a slight excess.

When proceeding according to process variant a) sometimes a hydrohalide of the desired compound is formed, thus it may optionally be necessary to liberate the base from its salt.

For this purpose an-alkali br alkaline earth metal hydroxide, carbonate or bicarbonate, furthermore aqueous ammonia can be used.

Aqueous ammonia is a particularly preferred reagent to liberate the base.

The bases of the general formula (I) can be converted into their physiologically acceptable acid addition salts by reacting them with an appropriate organic or mineral acid. For this purpose - primarily hydrochloric, hydrobromic, sulfuric, phosphoric, maleic, fumaric, or D-tartaric acid can be used.

The new compounds of die general formula (I) are valuable therapeutics. They exert a high inhibiting effect on the gastric acid secretion in rats, and also inhibit the appear ance of experimental ulcers. A significant advantage of the new compounds is, in comparison with the known substances capable of inhibiting the gastric acid secretion, that they are completely devoid of parasympatholytic (anticholinergic) side effects; thus no anticholinergic phenomena, such as mouth thickness, xnydriasis, accommodation disorders, etc., take place upon the administration of the new compounds.

The effect of the new compounds exerted on the gastric acid secretion and Shay ulcer was examined according to the method of H.

Shay et al. (Gastroenterology 5, 43/1945/), while their inhibition effect exerted on immobilisation and insulin ulcer was tested according to the method of Borsi et al. (Acta
Pharm. Hung. 38, 151/1968/). The mydriatic effect of the new compounds was tested according to the method of P. Pulewka (Arch. f.

exp. Path. u. Pharm. 168, 307/1932/), in order to decide whether they possess anticholinergic side effects or not. All experiments were carried out on rats. As reference substance, methantheline (diethyl-/2-hbdroxy- ethyl/-methylammonium bromide xanthene-9 carboxylate) was used. The results of the above tests are summarized in Table 1. TABLE 1
Inhibition of Anticholinergic Acute toxicity
Compound gastric juice Ulcer-inhibiting effect effect, LD50 LD50 mg., kg.

(No. of secretion, ED50 ED50 mg./kg.p.o. ileum Pulewka
Example) mg./kg. p.o. Shay immob. insulin γ/ml. mg./kg. p.o. i.p.

1 19 > 40 > 40 30 > 1 > 100 1700 510 2 12 > 40 30 20 > 1 > 100 270 150 3 16 > 40 > 40 35 > 1 > 100 390 310 4 22 28 30 18 > 1 > 100 460 230 6 40 > 40 > 40 20 > 1 > 100 1500 560 8 40 > 40 > 40 > 40 > 1 > 100 2000 100 10 15 > 40 40 40 > 1 > 100 580 310 11 18 > 40 > 40 5 > 1 > 100 520 300 12 20 > 40 > 40 > 40 > 1 > 100 1800 470 13 15 > 40 > 40 > 40 > 1 > 100 570 450 14 30 > 40 > 40 40 > 1 > 100 1500 800
Methantheline (reference) 20 15.2 20.7 11.5 3x10-5 17 320 76
The data of Table 1 clearly indicate that both the oral and the intraperitoneal toxicities of the compounds according to the invention are substantially lower than those of methantheline, used as reference substance.For some compounds the difference in toxicities reaches almost one order of magnitude in favour of the compounds according to the invention. Moreover, the therapeutical indices of the compounds according to the invention are generally more favourable than those of methantheline.

Consequently, the compounds according to the invention have several advantages over the hitherto known secretion inhibiting therapeutics: i.e. they have no anticholinergic side effects, their toxicities are low, and their therapeutical indices are favourable.

A part of the new compounds has, in addition to the secretion and ulcer inhibiting effects, considerable anti-inilammatory effect as well. With regard to the anti-intiammatory effect the simultaneous existence of the ulcerinhibiting effect is very favourable, since it is known that the general side effect of the antieinflammatory substances applied in the therapy so far is the induction of gastric ulcer.

The effective daily dosage of the compounds having the general formula (I) ranges from 10 mg. to 500 mg.

The anti-inflammatory activity of the new compounds was examined on rats, with
Winter's carrageen oedema test (Proc. Soc.

Exp. Med. 111, 544/1962/). 0.1 ml. of a 10% carrageen solution was injected into the hind paw of rats, and the increase in volume was measured three hours after this treatment.

The compounds under examination were administered orally, in a dosage of 100 mg./kg.

The results of this test are summarized in

Table 2.

TABLE 2
Compound Dosage Percentage (No. of Example) mg./kg. p.o. inhibition of oedema
1 100 37
2 100 40
3 100 61
4 100 58
6 100 37
9 100 32
10 100 40
11 100 18
14 100 50
The two most active compounds twos. 3 and 4) have been subjected to further tests.

It has been found that rhe EDso value of compound 3 in the carrageen oedema test with intraperitoneal administration is 110 mg./ kg., for compound 4 a value of 70 mg./kg.

has been obtained. The ED50 value of phenylbutazone (4-butyl-1,2-diphenyl-pyrazolidine3,5-dione) is 40 mg./kg. in the same test.

The anti-inflammatory activity of compound 4 has also been examined by means of the cotton granuloma test, according to Winter's method (J. Pharmacol. Exp. Ther. 141, 369/
1963/). In this test the EDt, value of the compound has been found to be 45 mg./kg./ day, on the basis of a one-week intraperitoneal treatment. The ED,,-values of phenylbutazone, determined in the same test, are as follows:
25 mg./kg./day 15%
50 mg./kg./day 19%
100 ing./kg./day -23% (see Arzneim. Forsch. 22, 2099/i972/).The EDso value could not be determined for phenylbutazorle, because all the test animals perished upon the administration of a 100 mg./kg. dosage of phenylbutazone for one week.

The compounds of the general formula (I) or their pharmaceutically acceptable acid addition salts can be administered into humans or animals in the form of pharmaceutical compositions, such as tablets, coated tablets, pills,
apsules, solutions, suspensions, injectable preparations, suppositories, etc. These pharmaceutical compositions are prepared by known methods, using the conventional pharmaceuti- cal carriers, diluents and/or auxiliary agents.

The pharmaceutical compositions can be sterilized, if required.

The invention is elucidated in detail with the aid of the following non-limiting Examples.

Example 1.

Preparation of N- (4-3'-pyndyl/-thiazol-
2-yl)-urea.

Method "A":
A mixture of 5.7 g. of 3-bromoacetylpyridine hydrobromide, 3.6 g. of thiobiuret and 50 ml. of water is maintained at 95 C for 2 hours. The solution is filtered when hot, the filtrate is heated again to 950 C, then rendered alkaline with 25% aqueous ammonia under vigorous stirring. The solution is cooled with ice water, and the separated product is filtered off. 3.9 g. (91%) of N-(4-/3' pyridyi/-thiazol-2-yl)-urea are obtained; m.p.: 3183190 C.

Method " B ":
A solution of 5.7 g. of trifluoroacetic acid in 25 ml. of dry toluene is added, within 2 hours, to a 4550 C suspension of 4.45 g.

of 2-amino-4- (3'-pyridyl) -thiazole (J. Heterocyclic Chem. 7, 1139/1970/) and 3.25 g. of sodium cyanate in

75 ml. of dry toluene, under vigorous stirring. When the addition is complete, the mixture is boiled for 2 hours, thereafter it is cooled, and the toluene is decanted. The residue is treated with 150 ml.

of 4% hydrochloric acid, the mixture is filtered, and the pH of the filtrate is adjusted to 9 with 8% aqueous ammonia. The separated precipitate is filtered off, dried, and recrystallized from acetone. 3.45 g. (63%) of N (4-/3'-pyridyl/-thiazol-2-yl)-urea are obtained; m.p.: 3163180 C.

Example 2.

Preparation of 1-isoproyl-3- (4'-/3"-
pyridyl/-thiazol-2'-yl)-urea.

A mixture of 5.32 g. of 2-amino-4- (3'pyridyl)-thiazole, 13 ml. of dry dimethylsulphoxide, 0.5 ml. of dry triethylamine and 3.4 g. of isopropyl isocyanate is heated at 100 C for 2 hours, thereafter the solution is poured into 50 ml. of cold water. The obtained product is filtered off, washed with water, and dried at 100 C. 6.4 g. (81%) of 1 - isopropyl - 3 - (4' - /3" - pyridyl/thiazol-2'-yl)-urea are obtained; m.p.: 297 301 C (after recrystallization from methylethyl ketone).

Examples 3 to 9.

The procedure described in Example 2 is repeated, but the following isocyanates are used as reactants: methyl isocyanate, ethyl isocyanate, n-propyl isocyanate, n-butyl isocyanate, cyclohexyl isocyanate, phenyl isocyanate, and p-chlorophenyl isocyanate. The obtained products are listed in Table 3.

TABLE 3
No. of
Example Product M.p. C
3 1-Methyl-3-(4'- '3"-pyridyl/-thiazol-2-yl)-urea 310-313
4 1-Ethyl-3-(4'-/3"-pyridyl/-thiazol-2-yl)-urea 312-314
5 1-(n-Propyl)-3-(4' -/3 "-pyridyl/-thiazol-2-yl)-urea 172-174
6 1-(n-Buty l)-3-(4 '-.'3 "-pyridyl/-thiazol-2-yl)-urea 182-188
7 1-Cyc lohexyl-3-(4' -/3 "-pyrilyl/-thiazol-2-yl)-urea 226-228
8 1-Phenyl-3-(4'-'3"-pyridyl/-thiazol-2-yl)-urea 314-316 9 1-(p-Chlorophenyl)-3-(4'-/3' "-pyridyl '-thiazol-2-yl)-urea 303-306
Example 10.

Preparation of 1 -ethyl-3-methyl-3- (4'-/3"-
pyridyl/-thiazol-2-yl) -urea.

A mixture of 3.83 g. of 2-methylamino-4 (3'-pyridyl)-thiazole (m.p.: 114-116 C, prepared by reacting 1-methylthiourea with 3-bromoacetylpyridine hydrobromide), 0.5 ml.

of dry triethylamine, 40 ml. of dry 1,2dimethoxyethane and 2.2 g. of ethyl isocyanate is refluxed for 6 hours. The solvent is evaporated under reduced pressure, and the residue is recrystallized from a mixture of isopropanol and petroleum ether. 3.9 g. (74%) of l - ethyl - 3 - methyl - 3 - (4' - /3" pyridyl/-thiazol-2'-yl)-urea are obtained; m.p.: 142-145 C.

Example 11.

Preparation of 1-isopropyl-3 -methyl-3-
(4'-/3"-pyridyl/-thiazol-2'-yl) -urea.

The procedure described in Example 10 is repeated but 2.55 g. of isopropyl isocyanate are substituted for ethyl isocyanate. 4.68 g.

(85%) of 1-isopropyl-3 -methyl-3- (4'-/3"- pyridyl/-thiazol-2'-yl)-urea are obtained; m.p.: 105-108 C (after recrystallization from benzene).

Example 12.

Preparation of 1-cyclopropyl-3-methyl- (4'-/3 "-pyridyl/-thiazol-2'-yl)-thiourea.

Step " A": Preparation of cyclopropyl isocyanate.

66 ml. of carbon disulphide are added to a solution of 43.2 g. of sodium hydroxide in 100 ml. of water, and the mixture is cooled to + 10 C in an ice bath. 61.6 g. of cyclopropylamine are added to the mixture within 25 minutes, under stirring, and the mixture is stirred for an additional 0.5 hour. Thereafter the mixture is heated to 80 C, and stirred at this temperature for 2 hours. The mixture is cooled to room temperature, 105 ml.

of ethyl chloroformate are added within 0.5 hours, and the obtained mixture is stirred for 0.5 hours at room temperature. Thereafter the upper oily phase is separated and the aqueous phase is extracted with ether. The ethereal layer is combined with the oily phase, dried, and the solvent is evaporated under reduced pressure. The residue is distilled in vacuo. 63.2 g. (58.5%) of cyclopropyl isothiocyanate are obtained; b.p.: 105-107
C/160 mm. Hg.

Step "B": Preparation of 1-cyclopropyl-3methyl - 3 - (4' - /3" - pyridyl/ - thiazol 2'-yl) -thiourea.

A mixture of 11.5 g. of 2-methylamino-4-
(3'-pyridyl)-thiazole, 30 ml. of dry 1,2dimethoxyethane, 1.5 ml. of dry triethylamine and 8.4 g. of cyclopropyl isothiocyanate is refluxed for 5 hours, then maintained in refrigerator overnight. The obtained crystalline substance is separated. 12.56 g. (72%) of 1 - cyclopropyl - 3 - methyl - 3 - (4' - /3"pyridyl/ - thiazol - 2' - yl) - thiourea are obtained; m.p.: 136-139 C (after recrystallization from 1,2-dimethoxyethane).

Examples 13 to 16.

The procedure described in step "B" of
Example 12 is repeated, but 2-amino-4-(3'pyridyl)-5-methyl-thiazole is substituted for 2-amino-4- (3'-pyridyl)-thiazole, and allyl isothiocyanate, methyl isothiocyanate and benzyl isothiocyanate, respectively, are substituted for cyclopropyl isothiocyanate. The obtained products are listed in Table 4.

TABLE 4
No. of
Example Product M.p. OC 13 1 ,3-Dimethyl-3-(4 ' - '3 '-'-pyn.dyl/-thiazol-2' -yl)-
thiourea 168-169
14 1-Cyclopropyl-3-(4'-/3"-pyridyl/-5-methyl
thiazol-2'-yl)-thiourea 258-261
15 l-Benzyl-3-me thyl-3-(4 '-/3 "-pyridyl/-thia zol-2 '-yl)-
thiourea 181-182
16 1-Allyl-3-methyl-3-(4'-/3"-pyridyl/-thiazol-2'-yl)
thiourea 105-110
Example 17.

Preparation of 1-phenyl-3- (4'-/3"-pyridyl/ thiazol-2'-yl) -urea.

Step "A" Preparation of 4-(3'-pyridyl)thiazole-2-carboxylic acid hydrazide
15 ml. of 72% hydrazine hydrate are added to a solution of 14.2 g. of ethyl-4-(3'-pyridyl)thiazole-2-carboxylate in 60 ml. of methanol.

A red solution is formed, and the crystalline product separated within some minutes. The crystals were filtered off. 12.25 g. (93%) of 4 - (3' - pyridyl) - thiazole - 2 - carboxylic acid hydrazide are obtained; m.p.: 176-180
C (after recrystallization from isopropanol).

Step "B": Preparation of 4-(3'-pyridyl)thiazole-2-carboxylic azide.

1 ml. of 37% aqueous hydrochloric acid is added to a suspension of 2.2 g. of 4-(3'pyridyl)-thiazole-2-carboxylic acid hydrazide in 25 ml. of water, and a solution of 0.7 g.

of sodium nitrite in 5 ml. of water is added dropwise to the stirred mixture under cooling in an ice bath. A yellow suspension is obtained.

After 15 minutes of stirring the separated product is filtered off and dried at 300 C.

2.15 g. (93%) of 4-(3'-pyndyl)-thiazol-2-yl carboxylic azide are obtained; m.p.: 1131190 C.

Step "C": Preparation of l-phenyl-3- (4'-/3"-pyridyl/-thiazol-2'-yl) -urea.

0.5 g. of 4-(3'-pyridyl)-thiazole-2-carboxy- lic azide, obtained as described in step B, are heated at 800 C in 5 ml. of dry benzene. When the gas evolution ceases, 0.4 g. of freshly distilled aniline and 0.1 ml. of dry triethylamine are added to the mixture, and the whole is heated at 80 C for additional 30 minutes. The mixture is cooled, and the separated substance is filtered off. 0.28 g.

(46%) of 1 - phenyl - 3 - (4' - /3" pyridyl/-thiazol-2'-yl) -urea are obtained; m.p.: 298306 C (after recrystallization from a mixture of dimethyl- formamide and ethanol).

The mixture of this compound with that prepared by reacting 4-(3'-pyridyl)-2-aminothiazole with phenyl isocyanate melts at 296304 C; thus both reactions yield the same product.

Example 18.

Preparation of l-(n-butyl)-3-(4'-/3"-
pyridyl/-thiazol-2'-yl) -urea.

The procedure described in step C of
Example 17 is repeated but n-butylamine is substituted for aniline. 0.24 g. (43%) of the desired compound are obtained; m.p.: 180- 185 C.

Example 19.

Preparation of 1-methyl-3-(4'-/3"
pyridyl/-thiazol-2'-yl)-urea.

A mixture of 5.7 g. of 3-bromoacetyl
pyridine hydrobromide, 4.0 g. of 1-methyl-4
thiobiuret (Ber. 25, 750/1892/) and 40 ml. of
water is stirred at 95 C for 1 hour. The
solution is filtered when hot, and the pH of the
filtrate is adjusted to 8.5 with 8% aqueous
ammonia. The separated product is filtered off,
washed with water, and dried at 60 C. 3.8 g.

(81%) of 1 - methyl - 3 - (4' - /3"
pyridyl/-thiazol-2'-yl)-urea are obtained; m.p.: 309313 C.

Example 20.

Preparation of 1-ethyl-3-(4'/3" pyridyl/-thiazol-2'-yl)-urea.

The procedure described in Example 19 is repeated with the difference that l-ethyl-4- thiobiuret (Ber. 25, 750/1892) is used as reactant. 3.67 g. (74%) of the desired compound are obtained; m.p.: 311315 C.

Example 21.

Preparation of 1-phenyl-3- (4'-/3"-
pyridyl/-thiazol-2'-yl) -urea.

The procedure described in Example 19 is repeated with the difference that l-phenyl-4thiobiuret (J. Am. Chem. Soc. 51, 2223/ 1929/) is used as reactant. 4.80 g. (80%) of the desired compound are obtained;

A mixture of 5.7 g. of 3-bromoacetyl pyridine hydrobromide, 4.0 g. of 1-methyl-4 thiobiuret (Ber. 25, 750/1892/) and 40 ml. of water is stirred at 95 C for 1 hour. The solution is filtered when hot, and the pH of the filtrate is adjusted to 8.5 with 8% aqueous ammonia. The separated product is filtered off, washed with water, and dried at 60 C. 3.8 g.

(81%) of 1 - methyl - 3 - (4' - /3" pyridyl/-thiazol-2'-yl)-urea are obtained; m.p.: 309313 C.

Example 20.

Preparation of 1-ethyl-3-(4'/3" pyridyl/-thiazol-2'-yl)-urea.

The procedure described in Example 19 is repeated with the difference that l-ethyl-4- thiobiuret (Ber. 25, 750/1892) is used as reactant. 3.67 g. (74%) of the desired compound are obtained; m.p.: 311315 C.

Example 21.

Preparation of 1-phenyl-3- (4'-/3"- pyridyl/-thiazol-2'-yl) -urea.

The procedure described in Example 19 is repeated with the difference that l-phenyl-4thiobiuret (J. Am. Chem. Soc. 51, 2223/ 1929/) is used as reactant. 4.80 g. (80%) of the desired compound are obtained; m.p.: 310-316 C.

WHAT WE CLAIM IS:
1. Substituted thiazolylurea or -thiourea derivatives of the general formula (I) or pharmaceutically acceptable acid addition salts thereof,

wherein
R1 stands for a pyridyl group,
R2 and R3 each stand for hydrogen or an alkyl group having from 1 to 4 carbon atoms,
Y stands for oxygen or sulphur, and
R4 and R5 each stand for hydrogen, an alkyl group having from 1 to 4 carbon atoms, allyl group, a C3~,; cycloalkyl group, phenyl group or a halophenyl group, or
R4 and R6 may form together with the adjacent nitrogen atom a heterocyclic group of the general formulae (X) or (XI),

wherein
n represents an integer of from 4 to 7, and
Z stands for oxygen, or an =NH, =N-CH3; or =N-C5H6 group.

2. A process for the preparation of substituted thiazolylurea or -thiourea derivatives of the general formula (I) or pharmaceutically acceptable acid addition salts thereof,

wherein
R1 stands for a pyridyl group,
R2 and R3 each stand for hydrogen or an

alkyl group having from 1 to 4 carbon
atoms,
Y stands for oxygen or sulphur, and
R4 and R5 each stand for hydrogen, an alkyl
group having from 1 to 4 carbon atoms,
allyl group, a C, cycloalkyl group,
phenyl group or a halophenyl group, or
R4 and R5 may form, together with the
adjacent nitrogen atom, a heterocyclic
group of the general formulae (X) or
(XI),

wherein
n represents an integer of from 4 to 7,
and Z stands for oxygen, or an =NH,
=N-CH, or =N-C,W group, in which
a) a haloacylpyridine hydrohalide of the general formula (II),

wherein
R 1and R2 each have the same meanings
as defined above and X stands for halogen,
is reacted with a compound of the general
formula (III),

wherein
R", R4, R and Y each have the same mean
ings as defined above, or
b) a 2-amincthiazolc of the general formula (IV),

wherein
R1, R2 and R3 each have the same meanings
as defined above, is reacted with an iso
cyanate or isothiocyanate of the general
formula (V),

wherein
R4, R5 and Y each have the same meanings
as defined above, or
c) a 2-aminothiazole of the general formula (IV), wherein Rl, R2 and R3 each have the same meanings as defined above, is reacted with an alkali metal cyanate or thiocyanate in the presence of a strong mineral or organic acid, or
d) a thiazol-2-yl-carbaminate or -thiocarbaminate of the general formula (VI),

wherein
R1, R2 and Rz each have the same meanings
as defined above and R6 stands for an
alkyl group having 1 to 4 carbon atoms
or a phenyl group, is reacted with an
amine of the general formula (VII),

wherein
R4 and R each have the same meanings
as defined above, or
e) a thiazole-2-carboxylic azide of the general formula (VIII),

wherein
R and K each have the same meanings
as defined above, is converted by heat
treatment into a thiazol-2-yl-isocyanate of
the general formula (IX),

wherein
R1 and R2 each have the same meanings
as defined above and Y stands for oxygen,
and this compound is reacted, preferably
directly in the reaction medium, with an
amine of the general formula (VII),
wherein R4 and R6 each have the same
meanings as defined above, or
f) a 2-aminothiazole of the general formula (IV), wherein R1 and R2 each have the same meanings as defined above and Ra stands for hydrogen, is reacted with carbon disulphide and dicyclohexyl carbodimide, and the obtained thiazol-2-yl-isothiocyanate of the general formula (IX), wherein R1 and R2 each have the same meanings as defined above and Y stands for sulphur, is reacted with an amine of the general formula (VII), wherein R4 and R5 each have the same meanings as defined above, or
g) a compound of the general formula (XII),

wherein
Rl, R2, R3 and Y each have the same meanings as defined above, is reacted with an amine of the general formula (VII), wherein R4 and R" each have the same meanings as defined above, or
h) a 2-aminothiazole of the general formula IIV), wherein R', R2 and R3 each have the same meanings as defined above, is reacted with a carbamoylchloride or tricarbamoylchloride of the general formula (XIII),

wherein
R' and R each have the same meanings as
defined above, and, of desired, a free
base of the general formula (I) is con
verted into its pharmaceutically accept
able acid addition salt, or a salt is
converted into the free base.

3. Pharmaceutical compositions containing a substituted thiazolylurea or -thiourea derivative of the general formula (I) or a pharmaceutically acceptable acid addition salt thereof, wherein Rl, R2, R3, R4, Ro and Y each have the same meanings as defined in claim 1, together with a carrier, diluent and/or auxiliary agent.

4. A process for the preparation of pharmaceutical compositions, in which a substituted thiazolylurea or -thiourea derivative of the general formula (I) or a pharmaceutically acceptable acid addition salt thereof, wherein R', R2, R3, R4, R5 and Y each have the same meanings as defined in claim 1, is admixed with a carrier, diluent and/or auxiliary agent.

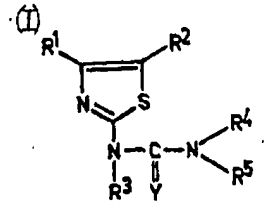
5. Compounds of the general formula (I), substantially as hereinbefore described in any one of the Examples.

6. A process for the preparation of compounds of the general formula (I), substantially as hereinbefore described in any one of the
Examples.

7. A compound of the general formula (I), whenever prepared by the process of claim 2 or claim 6.

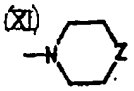
Az adatok az esp@cenet adatbázisból származnak - l2

(I)



(X)

(XI)



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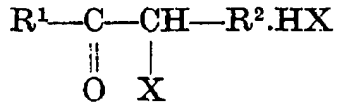

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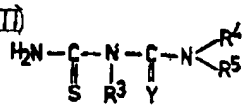

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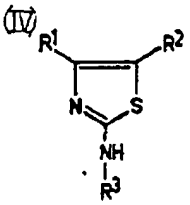

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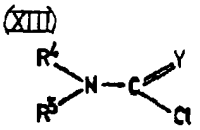

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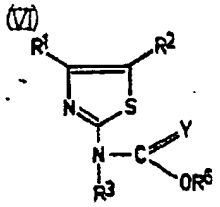

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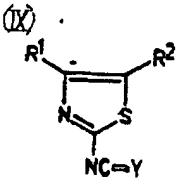

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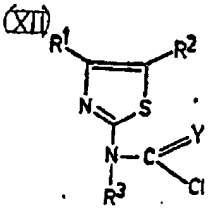

(VIII)